IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Hector Knight Castro et al. Art Unit 1618
Serial No. 10/510,454
Filed: October 4, 2004
Confirmation No. 2287
For: METHOD FOR OBTAINING A 2-18F-FLUOR-2-DEOXY-D-GLUCOSE 18F-FDG-SOLUTION
Examiner: Melissa Jean Perreira

APPEAL BRIEF

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May 17, 2010

APPEAL BRIEF

This is an appeal from the final rejection of the pending claims made in the final Office action dated July 16, 2009. A Notice of Appeal and Pre-Appeal Brief Request for Review were filed on October 16, 2009. The Office issued its Pre-Brief Appeal Conference Decision on April 15, 2010 and determined that the application remains under appeal because there is at least one actual issue for appeal.

I. REAL PARTY IN INTEREST

The real party in interest in connection with the present appeal is Mallinckrodt Inc. of 675 McDonnell Boulevard, Hazelwood, Missouri 63042.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any pending appeals, which may be related to, would directly affect, or would be directly affected by, or have a bearing on, the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 2 and 5-18 are pending. Claims 6-15 were previously withdrawn for being directed to a non-elected species and/or invention. Claims 3 and 4 were cancelled during

prosecution of this application. A copy of the claims involved in this appeal appears in the Claims Appendix of this Brief.

Claims 1, 2, 5 and 16-18 are currently rejected by the Office. The rejection of claims 1, 2, 5 and 16-18 is being appealed.

IV. STATUS OF AMENDMENTS

No amendments have been filed after the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary correlates claim elements to specific embodiments described in the application specification, but does not in any manner limit claim interpretation. Rather, the following summary is provided only to facilitate the Board's understanding of the subject matter of this appeal.

With reference to the present specification, independent claim 1 is directed to a method for improving the radiostability of a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution during autoclaving. The method comprises providing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution and adding at least one buffer based on a weak acid to the ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution. (See, for example, p. 2, lines 17-22, of the application as filed.) The buffer is selected from the group consisting of citrate, acetate, ascorbate and combinations of these compounds. (See, for example, p. 2, lines 23-32, of the application as filed.) The buffered ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution is then autoclaved. (See, for example, p. 3, lines 1-11, of the application as filed.)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants appeal the following rejections:

Appellants appeal the rejection of claims 1, 2, 5 and 16-18 under 35 U.S.C. § 103(a) as being obvious over the Manual and Operating Instructions, Nuclear Interface GmbH including the Supplement to the Manual and Operating Instructions entitled "FDG Synthesizers" in view of Damhaut et al. (U.S. Patent No. 6,172,207), Asai et al. (U.S. Patent No. 5,536,491) and Stone-Elander et al. (U.S. Patent No. 5,308,944).

VII. ARGUMENT

The Office has not Established that the Manual and the Supplement are Prior Art

The pending claims are rejected under 35 U.S.C. § 103(a) as being obvious over the Manual and Operating Instructions, Nuclear Interface Gmbh ("the Manual") including the Supplement to the Manual and Operating Instructions entitled "FDG Synthesizers" ("the Supplement") in view of Damhaut et al. (U.S. Patent No. 6,172,207), Asai et al. (U.S. Patent No. 5,536,491) and Stone-Elander et al. (U.S. Patent No. 5,308,944).

The Manual and Supplement were submitted by a third party during prosecution of the corresponding European patent application. The Manual and Supplement were submitted without any details or supporting documentation relating to their origin.[1] The Manual and Supplement were disclosed to the Office by Appellant in an Information Disclosure Statement dated December 4, 2006.

The Office relies upon the Manual and Supplement for disclosing the heating of fluor-deoxy-glucose (FDG) with a buffer to a temperature of 135°C. However, the Office has not established that the Manual and Supplement are a "Printed Publication" and are prior art under 35 U.S.C. §102(a) or 35 U.S.C. §102(b) against the pending claims of the present patent application.

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1 The European Patent Office did not consider the Manual and Supplement to be prior art. Specifically, the European examiner stated in the European Patent Office's July 18, 2008 Office action that the Manual and Supplement "cannot be considered as having been made available to the public. In particular, the circumstances of the alleged distribution (prior use) have not been sufficiently substantiated. Therefore, the examining division does not intend to further investigate the matter."

To establish that the Manual and Supplement are prior art, the Office must establish that these materials were **actually disseminated** as set forth in case law and by the Manual of Patenting Examining Procedure ("MPEP"). "A reference is proven to be a 'printed publication' upon a satisfactory showing that such document has been disseminated or otherwise made available." *In re Wyer*, 655 F.2d 221, 227, 210 USPQ 790, 795 (CCPA 1981). *In re Wyer* is cited in MPEP §2128, and further states that "the one who wishes to characterize the information, in whatever form it may be, as a 'printed publication' . . . should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art." The Office has simply failed to do so here.

Furthermore, there are numerous conceivable situations that explain the existence of the Manual and the Supplement but which do not support a conclusion that these materials were actually disseminated. For example:

- the document could be an internal draft of the manual, or a draft of a revision to the manual, that was not disseminated before being further revised;
- the document could be a revision (the document states "Last Revision: 10.12.2001" on its cover) of the manual and Nuclear Interface GmbH internally decided not to provide the manual to customers because, for instance, (i) the design of the dispensing unit was changed before the document was disseminated, or (ii) the manual had incorrect information;
- the document could be a revision of the manual, and sales of the dispensing unit were discontinued before it was disseminated; and/or,
- the document could be a fabrication by the third party who submitted it the EPO and therefore was never produced by Nuclear Interface GmbH.

In spite of numerous plausible examples of why the document may not have in fact been published, the Office has failed to establish that the document was actually disseminated (to customers of Nuclear Interface GmbH or otherwise).

Applicants additionally submit that, even assuming *arguendo* that the document was disseminated, the Office has not established that dissemination of the document was not subject to a **confidentiality agreement**. (See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*,

908 F.2d 931, 15 USPQ2d 1321 (Fed. Cir. 1990), cited at MPEP §2128.01. In this case, four reports on the AESOP-B military computer system, which were not under security classification, were distributed to about fifty organizations involved in the AESOP-B project. One document contained the legend *"Reproduction or further dissemination is not authorized."* The other documents were of the class that would contain this legend. The documents were housed in Mitre Corporation's library. Access to this library was restricted to those involved in the AESOP-B project. The court held that public access was insufficient to make the documents "printed publications."

In addition to failing to establish that the document was in fact disseminated, or that it was not disseminated subject to a confidentiality agreement, the Office has failed to establish that the document was disseminated prior to the effective filing date of the present application. More specifically, it is to be noted that the present application claims priority to a PCT patent application filed on April 23, 2003, which in turn claims priority to a European patent application filed April 24, 2002. The Manual lists October 12, 2001 as the "Last Revision" date. However, the Office has not established that the document was actually disseminated by a date effective to establish the document is a valid prior art reference under 35 U.S.C. §102(a) or 35 U.S.C. §102(b). (See, e.g., *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986), cited at MPEP §2128, wherein the court held that since there was no proof regarding whether a mailer was received by the public prior to the filing date of the application at issue, there could be no rejection under 35 U.S.C. §102(a). See also MPEP §2128, which states in reference to internet and on-line databases that "if the publication itself does not include a publication date (or retrieval date), it cannot be relied upon as prior art under 35 U.S.C. 102(a) or (b).")

In response to these arguments set forth by the Appellants, regarding the prior art status of the Manual and Supplement as prior art, the Office asserts that: (1) the scenarios offered by Appellants in which the Manual and Supplement were not disseminated are "hypothetical" and not based on any evidence, (2) the manual provides contact information including a phone number, fax number, website and email address which shows the manual was distributed to those skilled in the art, and (3) the references should be considered because Appellants have admitted that it is material to patentability by citing it in the December 4, 2006 Information Disclosure Statement.

Appellants submit that for the reasons set forth below, the Office's positions are clearly contrary to law.

Regarding the Office's assertions that the above-noted scenarios in which the Manual and Supplement were not distributed are only "hypothetical," **it is not the Appellants' burden** to establish that the document was not distributed, but rather **it is the Office's burden** to establish that the document was **actually distributed**. (See *In re Wyer*, 655 F.2d 221, 227, 210 USPQ 790, 795 (CCPA 1981) cited in MPEP §2128 ("the one who wishes to characterize the information, in whatever form it may be, as a 'printed publication' . . . should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art.").) Accordingly, the Office's opinion that the scenarios presented by the Appellants are merely hypothetical is not relevant to the issue. The **Office must establish that the reference was actually distributed, and it has simply failed to do so here**.

Further, recitation of contact information such as a phone number, fax number, website, and email address on the Manual and Supplement does not establish that the manual was actually disseminated or otherwise made available to those of skill in the art. In *Resqnet.com, Inc., v. Lansa, Inc.*, 533 F.Supp.2d 397 (S.D.N.Y 2008), *aff'd in part* 544 F.3d 860 (Fed. Cir. 2010), the alleged infringer argued that the patent at issue was invalid for being described in a printed publication before the critical date. The references at issue were a **user manual** that had a date of October 1991 on its first page and a tutorial that had a copyright date of 1993. According to the court, "no witness testified, nor was any evidence presented, that either of these documents was ever published or disseminated to the public." As a result, **the court held that, in the absence of such evidence that the references were actually published or made public prior to the critical date, the references could not be considered prior art.**

In view of the foregoing, the fact that the Manual being cited by the Office here includes a phone number, fax number, website and email is clearly not evidence that the reference was actually disseminated or otherwise made available. (*In re Wyer*, 665 F.2d 221, 227, 210 USPQ 790, 79 (CCPA 1981).)

Additionally, the alleged infringer in *Resqnet.com* also argued that submission by the patent owner of the references in an information disclosure statement during reexamination was an admission that the references were publicly disseminated. In contrast, the U.S. Patent Office noted, during the reexamination proceeding related thereto, that the "mere submission of an IDS to the USPTO does not constitute the patent Applicant's admission that any reference is in the IDS is prior art" (*Resqnet.com*, 533 F.Supp.2d 397, 414, note 5; citing *Abbott Lab. V. Baxter Pharm. Prods.*, 334 F.3d 1274, 1279 (Fed. Cir. 2003), emphasis added). Further, **according to**

the court, submission of the reference in the IDS does not speak to the dissemination of the reference prior to the critical date.

The District Court holding in *Resqnet* that submission of documents by a patent applicant in an information disclosure statement does not equate to an admission that the documents are prior art has been affirmed by the Federal Circuit. During review of the district court holding in *Resqnet.com*, the Federal Circuit agreed that "ResQNet did not convert these manuals into printed publication prior art by including them with the IDS submitted to the PTO." *Resqnet.com, Inc. v. Lansa, Inc.*, 594 F.3d 860, 866 (Fed. Cir. 2010). Further, the Federal Circuit was of the opinion that "no other evidence of publication or public availability was provided" even though the manual and tutorial at issue recited respective dates of October 1991 and 1993 thereon. *Id.*

With respect to the status of a reference as prior art as a result of it being submitted by Appellants in an IDS, it is to be noted that the court's position taken in *Resqnet.com*, as well as the position taken by the U.S. Patent Office during the reexamination proceeding detailed therein, is reinforced by rule. Specifically, the Office's attention is called to **MPEP §2129(IV)**, which clearly **states that the "[m]ere listing of a reference in an information disclosure statement is not taken as an admission that the reference is prior art against the claims."** (Emphasis added.) Furthermore, **37 CFR 1.97(h) states that "[t]he filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to the patentability as defined in § 1.56(b)."**

Accordingly, the Office's assertion that the Appellants "declared that the reference is considered material to patentability" based on the Appellants' citation on the Manual and Supplement in an information disclosure statement is clearly false and has been explicitly rejected by both the U.S. Patent office and the Federal Circuit Court of Appeals and is not relevant to whether the reference was actually distributed.

Independent Claim 1 and Claims Depending Therefrom are Not Obvious

Claim 1 is directed to a method for improving radiostability of a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution during autoclaving. The method of claim 1, as amended, comprises the steps of: (a) providing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution; (b) adding at least one buffer based on a weak acid consisting of citrate, acetate, ascorbate and combinations thereof to the ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution; and, (c) autoclaving the buffered ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution. As indicated in the specification (see, e.g., p. 2, lines 1-16 of the application), Appellants have discovered a method for preparing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that is sufficiently sterile and stable for use (i.e., for injection in a patient in need thereof). Sterilization is achieved by autoclaving a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution that has been sufficiently buffered with a solution of a weak acid. In this way, a sterilized solution is obtained that still meets the specification of more than 95% radiochemical purity eight hours after production.

The Office has based it obviousness rationale on (1) substitution of the citrate buffer of Damhaut et al. for the buffer disclosed in the Manual for improving the stability of a FDG solution, and (2) substitution of the autoclaving sterilization method of Asai et al. for the sterilization method of Damhaut et al. However, in view of Appellants' position that the Manual and Supplement are not prior art against the present application, Appellants will direct the remainder of their comments on the present rejection toward the combination of Damhaut et al., Asai et al and Stone-Elander et al., as this rationale does not fully rely on the use of the Manual as a prior art reference.

With respect to the Office's combination of Asai et al. with Damhaut et al., the Office seems to base its obviousness rationale on a simple substitution of one known element (autoclaving process of Asai et al.) for another (use of filtration to purify and sterilize) to obtain what the Office believes are predictable results. Under this rationale, to establish a *prima facie* case of obviousness, the Office must establish that: (1) the prior art contained a method which differed from the claimed method by the substitution of some steps with other steps; (2) the substituted components and their functions were known in the art; (3) that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and, (4) whatever additional findings based on the *Graham* factual

inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. MPEP §2143. Appellants submit that the Office has, at a minimum, not shown that the prior art contains a method which differed from the claimed method by the substitution of one or more steps therein, and/or that the one of ordinary skill in the art would have known to substitute one known element for another, and/or that the results of the substitution would have been predictable.

Damhaut et al. teach preparation of ^{18}F-FDG that is purified and sterilized. Notably, however, they indicate that **the pH of the final solution may be adjusted by adding a citrate or sodium phosphate buffer after purification and sterilization**. Accordingly, if the autoclaving step of Asai et al. were substituted for the filtration step of Damhaut et al. in order to achieve purification and sterilization, the buffer would be added after autoclaving of the solution. As a result, radiostability of ^{18}F-FDG would not be improved. Alternatively, one of ordinary skill in the art would have to find some motivation to rearrange the steps of Damhaut et al., in addition to substituting the autoclaving step of Asai et al. for the filtration step of Damhaut et al., and the Office has simply not established why there would be any such motivation to do so. In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. MPEP §2141.01.

Appellants further submit that the skilled artisan would not have combined the autoclaving step of Asai et al. into the ^{18}F-FDG preparation method of Damhaut et al., because **Damhaut et al. actually teach away from use of an autoclaving step**. Specifically, Damhaut et al. disparage the use of process steps that require heating. According to the abstract, the process of Damhaut et al. "is more rapid than conventional methods and is performed at room temperature rather than high temperature for conventional technology." According to Damhaut et al., such heating steps are undesirable as they add to the total preparation time (see col. 2, lines 9-15; col. 5, lines 66-67). The skilled artisan would not have combined the references regardless of any high-temperature stability of the ^{18}F isotope or FGD compound set forth in the Stone-Elander et al. reference or in the Manual. **It is improper to combine references where the references teach away from their combination. MPEP §2145.**

Appellants submit the Office has also failed to establish that the results of the substitution of the autoclaving step of Asai et al. for the filtering step of Damhaut et al. would be predictable. Assuming, *arguendo*, that the skilled artisan would rearrange the process steps of

Damhaut et al. such that the buffer were added prior to autoclaving, the Office has not set forth why the skilled artisan would expect the buffer to provide radiostability enhancing properties. Damhaut et al. disclose that a citrate or sodium phosphate buffer is added to adjust pH, not for improving radiostability of the solution. The Office has not established that this result would be predictable, and there is no other reasoning or articulation on record regarding motivation to rearrange the processing steps of Damhaut et al.

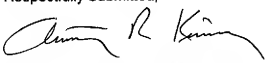
In response to Appellants' argument, the Office submits that the reference of Damhaut et al. was not used to teach autoclaving, but rather was used to teach a citrate buffered 18F-FDG solution for NMR. Regardless of what purpose the Office is using the reference, the fact that it teaches away from using an autoclaving step is still relevant. "A prior art reference must be considered in its entirety, i.e., as a whole, **including portions that would lead away from the claimed invention**." (See, e.g., MPEP §2141.02(VI), emphasis added.) The Office cannot pick and choose which portions of Damhaut et al. may be ignored, and the fact that Damhaut et al. teach away from using an autoclaving step must be considered by the Office.

In view of the foregoing, the Office has clearly failed to establish a *prima facie* case of obviousness. Appellants therefore submit that the subject matter of claim 1, as well as all claims depending therefrom, is patentable over the cited references, both alone and in combination.

CONCLUSION

For the reasons stated above, Appellants respectfully request that the Examiner's rejections be reversed and that the pending claims be allowed. The Commissioner is hereby authorized to charge any fees which may be required for this Appeal Brief to Deposit Account Number 13-1160 in the name of Mallinckrodt Inc.

Respectfully Submitted,



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VIII. CLAIMS APPENDIX

1. A method for improving radiostability of a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution during autoclaving, the method comprising:

a) providing a ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution,

b) adding at least one buffer based on a weak acid to the ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution, wherein the buffer is selected from the group consisting of citrate, acetate, ascorbate and combinations thereof; and,

c) autoclaving the buffered ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution.

2. The method according to claim 1, wherein the buffered ^{18}F-FDG-solution maintains radiochemical purity after being autoclaved, thus rendering the solution suitable for medical applications.

5. The method according to claim 1, wherein the pH of the citrate buffer is lower than 5.5.

16. The method of claim 2, wherein the radiochemical purity of the buffered ^{18}F-fluor-deoxy-glucose (^{18}F-FDG)-solution is at least 95%.

17. method accordingly to claim 16, wherein the radiochemical purity of the buffered ^{18}F-FDG-solution is at least about 95% eight hours after being autoclaved.

18. The method according to claim 5, wherein the pH of the citrate buffer is between 2 and 5.5.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.